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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Provisional Specification filed on 04/09/2003 in respect of Patent Application No.907/MUM/2003 of Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus". Sarkhej-Dholka Road, Bhat, Ahmedabad 382210, Gujarat. India, an Indian Company.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act. 1970.

Dated this 18/13 day of Dec 2006.

M.A. Haafeez

(M.A.HAAFEEZ)
ASSTT.CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT

(See section 5(52), 7, 54, AND 135 and Rule 33A)

1. We Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, an Indian Company.

2. Hereby declare:-
   a. That we are in possession of an invention for the **PROCESS FOR THE PREPARATION OF TRITYL LOSARTAN.**
   b. That the Provisional Specification relating to the invention is filed with this application.
   c. That there is no lawful ground of objection to the grant of patent to us.

3. Further declare that the inventors for the said invention are

   a. Dr. Bakulesh Mafatlal Khamar, 201, "Ashadha", Vasundhara Colony, Gulbai Tekra, Ellisbrige, Ahmedabad – 380006, Gujarat, India, Nationality, Indian.

   b. Mr. Indravadan Ambalal Modi, Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

   c. Madhusudana Rao (Gajula), Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

   d. Radha (Achanatha), Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

4. That we are the assignee of the true and first inventors

5. That our address for service in India is as follows: Dr. Bakulesh Mafatlal Khamar, Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India.

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907/MUM/2003

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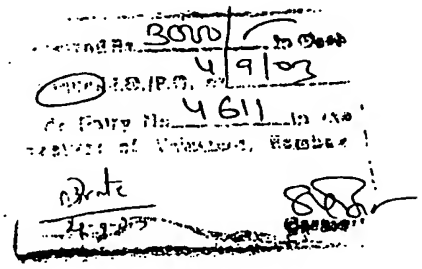


6. Following declaration was given by inventors:
We the true and first inventors for this invention declare that the applicant herein is our assignee

a. Dr Bakulesh Mafatlal Khamar, 201, "Ashadha", Vasundhara Colony, Gulbai Tekra, Ellisbridge, Ahmedabad - 380006, Gujarat, India, Nationality, Indian.

Dr. Bakulesh M Khamar
Date: August 19, 2003

b. Mr. Indravadan Ambalal Modi, Cadila Pharmaceuticals Limited, "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

Mr. Indravadan Ambalal Modi
Date: August 19, 2003

c. Madhusudana Rao (Gajula), Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

Madhusudana Rao (Gajula)
Date: August 19, 2003

d. Radha (Achanatha), Cadila Pharmaceuticals Ltd., "Cadila Corporate Campus", Sarkhej-Dholka Road, Bhat, Ahmedabad, 382210, Gujarat, India, Nationality, Indian.

Radha (Achanatha)
Date: August 19, 2003

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection of the grant of patent to us in this application.
8. Following are the attachment with this application:
   (a) Provisional specification (3 copies)
   (b) Statement and Undertaking on Form 3(3 copies)
   (c) Fees Rs. 3000/- (Rupees Three thousand only) in cheque bearing no. 005707 dated 09/07/2003 on Corporation bank.
9. We request that a patent may be granted to us for the said invention.

Dated, this August 19, 2003.

Dr. Bakulesh M Khamar
Director - Research
FOR CADILA PHARMACEUTICALS LIMITED.

To,
The Controller of Patents
The Patents Office Branch
Mumbai

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)
THE PROVISIONAL SPECIFICATION
(See section 10)

1. PROCESS FOR THE PREPARATION OF TRITYL LOSARTAN

2. CADILA PHARMACEUTICALS LTD., "CADILA CORPORATE CAMPUS", SARKHEJ-DHOLKA ROAD, BHAT, AHMEDABAD, 382210, GUJARAT, INDIA, AN INDIAN COMPANY.

3. THE FOLLOWING SPECIFICATION DESCRIBES AND ASCERTAINS THE NATURE OF THIS INVENTION AND THE MANNER IN WHICH IT IS TO BE PERFORMED.

ORIGINAL

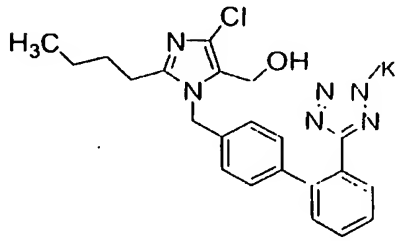
PROCESS FOR THE PREPARATION OF TRITYL LOSARTAN

FIELD OF THE INVENTION :

The present invention relates to the disclosure of an efficient ,novel and commercially feasible method of synthesis of Triphenylmethyl protected Losartan (herein abbreviated as" Trityl losartan") involving condensation of 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde (intermediate-A) and N-(Triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl]tetrazole(intermediate-B) using a base and phase transfer catalyst in biphasic solvent system followed by in-situ reduction using sodium borohydride.

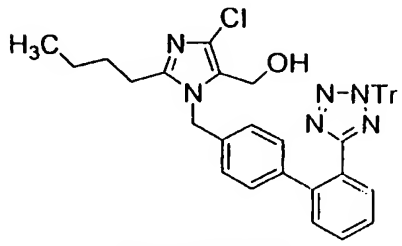
BACKGROUND OF THE INVENTION :

Losartan Potassium (abbreviated as "Losartan-K") is useful in the treatment of hypertension as an AT_1 selective angiotensin II antagonist. Losartan Potassium is 2-n-butyl-4-chloro-1-[[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt. CAS No. [124750-99-8] with structure represented by **Formula-1**



LOSARTAN - K **[Formula-1]**

"Losartan –K" is generally prepared from the intermediate-"Trityl Losartan" which is 2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2'-[(triphenylmethyl)tetrazol-5-yl]biphenyl-4yl]methyl]imidazole. CAS No. [133909-99-6] **[Formula-2]**.



Tr = TRITYL

TRITYL LOSARTAN **[Formula-2]**

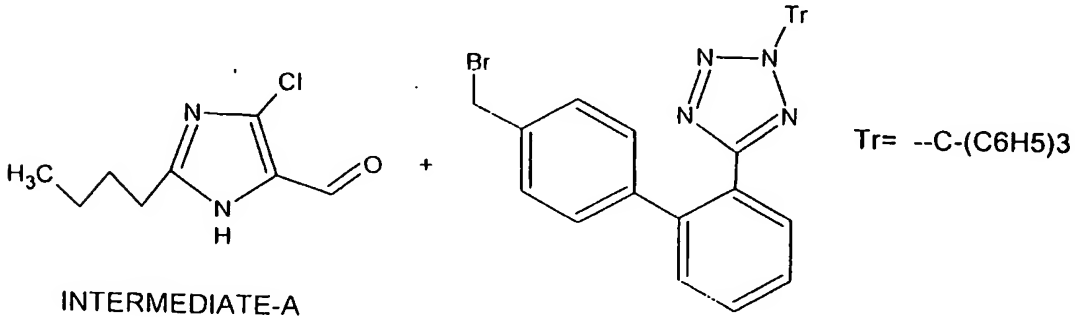
BACKGROUND OF INVENTION :

U.S. patent 5310928 describes the preparation of Losartan where 2-n-butyl-4-chloro-1H-imidazole-5-carboxaldehyde (intermediate-A) is coupled with 5-(4'-bromomethyl-1,1'-biphenyl-2-yl)-2-triphenylmethyl-2H-tetrazole (intermediate-B) in N,N-dimethyl acetamide as solvent and anhydrous potassium carbonate as a base to give 2-n-Butyl-4-chloro-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5yl)-1,1'-biphenyl-4-yl)methyl]-1H-imidazole-5- carboxaldehyde (intermediate-C). The intermediate-C is not isolated but reduced in situ with sodium borohydride to give "Trityl Losartan".

Intermediate-C can be extracted from the aqueous N,N-dimethylacetamide solution with toluene, concentrated and crystallized using ethyl acetate or ethanol as solvent.

The scheme of synthesis is described below.

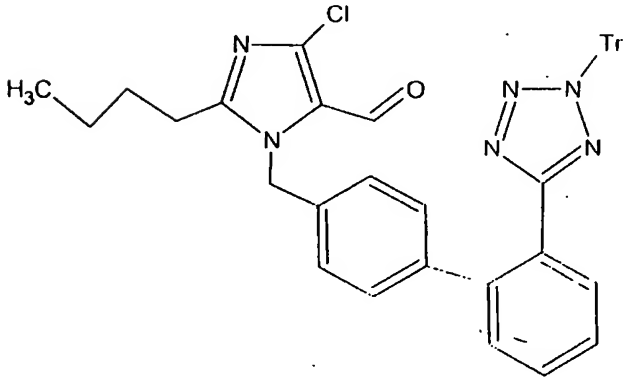
SYNTHESIS OF TRITYL LOSARTAN



INTERMEDIATE-A

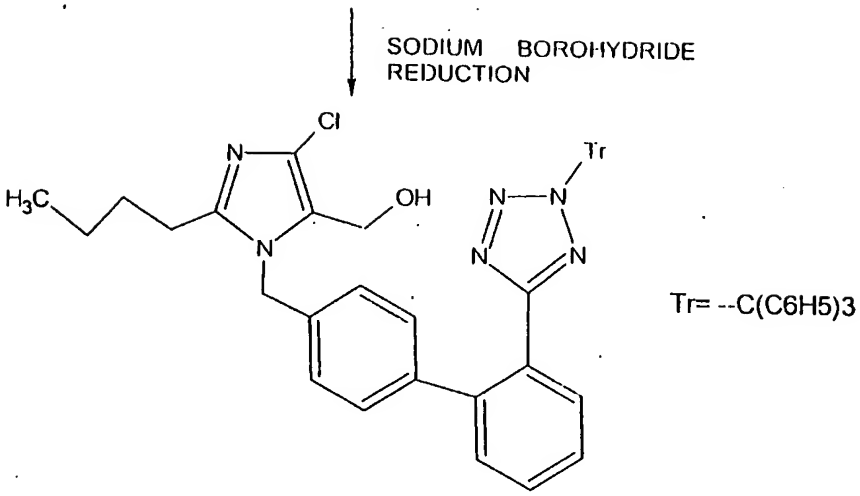
INTERMEDIATE-B

BASE / SOLVENT



Tr= --C(C6H5)3

INTERMEDIATE-C



" TRITYL LOSARTAN "

In a process disclosed in J. Med. Chem. (1991) 34 2525-2547 intermediate-C is prepared by coupling intermediates A and B in N.N-dimethylformamide using potassium carbonate as a base. The reported yield of intermediate C is as low as 49 % with respect to intermediate-A.

In an alternate process disclosed in J. Med. Chem. (1991) 34 2525-2547, " Trityl Losartan" is synthesized as follows:

To a mixture of intermediate A, tetrabutylphosphonium bromide ,10N aq. Sodium hydroxide, water
and methylene chloride, is added, a solution of intermediate B dissolved in methylene chloride.

The reaction mixture is stirred at 25 deg. C for 24 hr. Sodium borohydride is added and the mixture is stirred another 24 hr. Water is added and the layers are separated. The organic layer is washed with water and dried over anhydrous magnesium sulfate and filtered and the solvent is removed under vacuum to furnish material as yellow glass.. The glass is crystallized from nitromethane to provide 2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2'-[(triphenylmethyl)tetrazol-5-yl]biphenyl-4yl]methyl]imidazole – ["Trityl Losartan"] . The yield of "Trityl Losartan" with respect to intermediate B is 54 % . This process involved long reaction times and extensive multistep extractive work-up resulting in low yield.

DETAILED DESCRIPTION OF PRESENT INVENTION:

The aim of the present invention is to develop an improved process that eliminates the disadvantages of the prior art processes for synthesis of "Trityl Losartan" and also to eliminate extensive purification procedures to separate the regioisomer.

The coupling reaction between Intermediates A & B is carried out in presence of a base and phase transfer catalyst in an aqueous/organic biphasic solvent system where organic

solvent is selected from toluene, xylene, pentane, heptane, octane, cyclohexane etc. Preferably the reaction is carried out in toluene. The reaction temperature varies from 25 °C to reflux temperature of the solvent, preferably from 80 to 100°C.
The base employed is selected from any of the alkali metal hydroxides and preferably poassium hydroxide. The reaction mixture after condensation is allowed to settle. Aqueous Phase is removed and the organic phase is washed with water to remove any traces of phase transfer catalyst and base. The organic phase is diluted with an alcohol selected from C1-C4 alcohols, preferably Methanol and reduced with sodium borohydride.
On completion of the reaction, it is quenched by addition of water. Subsequent cooling of the reaction mass precipitates the "Trityl Losartan " which is then isolated by filtration. The purity of the product is 96% and is suitable for the production of Losartan potassium directly without any further purification.
This " One Pot" synthesis of "Trityl Losartan" simplifies the process and simultaneously gives high yield and purity of " Trityl Losartan ". The achieved yield of "Trityl Losartan " is 75.5 % with respect to intermediate B.

The present invention is illustrated by way of nonlimiting examples as follows.
Example-1
Toluene (5L) is charged into a 10 L round bottomed flask equipped with reflux condenser and a stirrer under nitrogen purging.To this is added N-(Triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole [1.0Kg: 1.795mol] and 2-n-butyl 4-chloro 1H-imidazol 5-carboxaldehyde [0.28 kg- 1.501 mol] under stirring. The reaction is stirred for 5 minutes and tetrabutylammonium bromide [0.01 kg: 0.03mol] is added and stirred for 10 minutes. A pre-formed solution of potassium hydroxide, was prepared by dissolving potassium hydroxide [0.12 kg, 2.13 mol] in water [0.6 L],is charged to the above reaction mass at room temperature under stirring. The reaction mixture is raised to 80-90 °C. and refluxed for 3.5 hours while the progress of the reaction is monitored by HPLC. When the reactant concentration is below 1.0%, the reaction mass is cooled to room temperature. Water [1.0 L] is added and stirred for 30 min. at room temp. Stirring is stopped and the layers are separated. The lower aqueous layer is discarded and the toluene layer is washed with water (2L). The aqueous layer is discarded and toluene layer is diluted with methanol (0.6 L). The solution is cooled to 0 °C and sodium borohydride (0.031 kg, 0.837 mol) is added in lots maintaining the temperature below 5 °C. Once the addition of sodium borohydride is complete, the reaction mixture is stirred for 3.5 hr. Progress of the reaction is monitored by HPLC. The reaction is stopped when aldehyde is less than 10% by addition of 3L water. The whole mass is stirred for 0.5h and the precipitated solid is filtered off. The wet cake is washed with toluene (0.5 L) and sucked dry. The product is dried at 70 °C until the moisture content is less than 1%. A second crop of the product can be isolated by concentration of the toluene layer. By this way "Trityl Losartan" is obtained as off-white solid.
Yield: 0.9 kg. [75.5%]
HPLC purity: 96%
^{1}H NMR ($CDCl_3$): δ 9.73(s, 1H,); 7.92 (m, 1H); 7.51-6.81 (m, 22H); 5.45(s, 2H); 2.49(t, 2H); 1.64(q, 2H); 1.28 (sextet, 2H); 0.86 (t, 3H)

The advantages of the present invention are summarized as follows.
The isolation of intermediate C is omitted to prevent quality loss.
This process does not require the separation of regioisomer of intermediate C and the isolation procedure does not involve extensive purification and multistep extraction.
This " One Pot" synthesis of "Trityl Losartan" simplifies the process and simultaneously gives high yield and purity of " Trityl Losartan ".
" Trityl Losartan" is prepared in 75.5% yield with respect to intermediate B and purity 96%.

Dated this August 19, 2003

Khamar B. M.

Dr. Bakulesh M Khamar